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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,024	12/12/2000	Brian Seed	08100/003003	5494

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/05/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/735,024	Applicant(s) SEED ET AL.	
	Examin r San-ming Hui	Art Unit 1617	

-- Th MAILING DATE of this communication app ars on th cover she t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendments filed July 30, 2002 have been entered.

The outstanding objection of claims 58 and 66 is withdrawn in view of the amendments filed July 30, 2002.

The outstanding rejections under 35 USC 112, first paragraph in regard to marine lipids is withdrawn in view the applicant's remarks and the teachings of Sassen et al.

The outstanding rejections under 112, second paragraph in regard to the phrase "compound comprising" is withdrawn in view of the amendments filed July 30, 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-60, 62-63, 65-68, and 70-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cholesterol synthesis or transfer inhibitor disclosed in page 7 in the specification, lines 3-12, does not reasonably provide enablement for other cholesterol synthesis or transfer inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is

directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines neither a "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor". Given that there is no common core structural, physical or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention.

Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor" examples are set forth, thereby failing to provide sufficient working examples. It is

noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "cholesterol ... transfer inhibitor" in claim 55 renders the claims indefinite as to the compounds encompassed thereby.

Response to arguments in regard to rejections under 35 USC 112

Applicant's rebuttal arguments averring the cholesterol synthesis or transfer inhibitors being well-known to one of skilled artisan have been considered, but are not found persuasive. Cholesterol synthesis or transfer inhibitors may be referred, from the expression, to compounds that inhibit the synthesis or the transfer of cholesterol. However, this expression only describes the function of the compounds, not the actual

compounds. The synthesis and the metabolic pathway of cholesterol are quite complex. Many different steps, locations, and enzymes are involved in those pathways. It is not clear what steps or enzymes are these compounds are intended to inhibit. Only one class of compounds called HMG-CoA reductase inhibitors are known as cholesterol synthesis inhibitors and there is no known compound as cholesterol transfer inhibitor. It is also not clear what transfer steps of cholesterol are inhibited: are the steps between the intestine and the liver? Or the steps between the liver and the blood stream? One of ordinary skill in the art would not know what cholesterol transfer inhibitor would be. Furthermore, one of ordinary skill in the art would not be able to ascertain compounds, which are only functionally described by the expression "Cholesterol synthesis or transfer inhibitors", suitable for practice the instant invention without undue experimentations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 55-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sassen et al. (Cardiovasc. Drugs ther., 1994; 8(2):179-191), Vane et al. (Circulation, 1991; 84(6):2588-2590), Lee et al. (Am. J. Cardiol., 1994; 73(15):1037-1040), Watts et al. (Lancet, 1992; 339(8793):563-569), and Demopulos et al. (US Patent 5,800,385), references of record mailed February 26, 2002.

Sassen et al. teaches fish oil, which contains eicosapentaeneoic acid and docosahexaeneoic acid, can cause atherosclerotic lesion regression and prevent progression of atherosclerosis (See particularly page 180, col. 1, first paragraph; and col. 2, last paragraph; also 186, col. 2 - 187, col. 1). Sassen et al. also teaches the dosages of eicosapentaeneoic acid and docosahexaeneoic acid used in the method of causing regression of atherosclerotic lesions and preventing progression of atherosclerosis are 100-700 mg/kg/day respectively (See page 183, Table 3 and page 184, Table 4). For an average 70kg adult, the dosage will be 7 – 49 g/day. Sassen et al. also teaches that the fish oil decreases the intimal thickness to 23 or 24 μm in comparison to 39μm treated by non-treated subject (See page 185, col. 1, first paragraph). Sassen et al. further teaches that fish oil also decrease the intimal proliferation with 54% and 46% decrease after 3 months of treatment (See page 185, col. 1, first paragraph).

Vane et al. teaches that 50 – 1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet inhibition (See page 2588, col. 1, last, paragraph and page 2589, col. 1, last paragraph).

Lee et al. teaches that 10mg of pravastatin and 1500mg of niacin daily are useful in prevention of restenosis (See the abstract).

Watts et al. teaches cholestyramine with lipid-lowering diet are useful in regression of atheroslcerosis by 66% (See particularly abstract and page 568, col. 1, second paragraph). Watts et al. also teaches that cholestyramine with lipid-lowering diet increasing coronary artery diameter as the LDL cholesterol concentration decreases (See page 568, col. 1, second paragraph; also col. 2, first paragraph). Watt et al. also teaches that patients taking cholestyramine with lipid-lowering diet can lowered the LDL concentration to about 1.71 mmol/l or 65.7mg/dl (1.71 mmol/l x 200mg/dl / 5.2mmol/l = 65.7mg/dl) (See page 567, col. 1, Fig. 1).

Demopulos et al. teaches buspirone is useful in an anti-restenosis method (See particularly the abstract, col. 13, line 9-10 and claims 1).

The references do not expressly teach the agents are useful together in a method of reducing coronary artery stenosis. The references do not expressly teach the LDL concentration to be less than 55 mg/dl. The references do not expressly teach the dosage of aspirin to be greater than 80 mg/day. The references do not expressly teach the dosage of buspirone to be between 10-80 mg/day.

It would have been obvious to one skill in the art when the invention was made to employ the agents herein together with lower-lipid diet in a method of reducing coronary

artery stenosis (narrowing). It would have been obvious to one skill in the art when the invention was made to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary artery stenosis. It would have been obvious to one skill in the art when the invention was made to lower the LDL concentration in the patient to below 55 mg/dl.

One of ordinary skill in the art would have motivated to employ the agents herein together with lower-lipid diet in a method of reducing coronary artery stenosis (narrowing) because all the agents herein are known to prevent or treat restenosis or cause vasodilatation. Therefore, combining two or more agents which are known to be useful to prevent or treat restenosis or cause vasodilatation individually into a method useful for reducing coronary artery stenosis or coronary artery narrowing is *prima facie* obvious.

One of ordinary skill in the art would have motivated to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary artery stenosis because the optimization of result effect parameters (e.g., dosage range) is obvious as being within the skill of the artisan, absent evidence to the contrary.

One of ordinary skill in the art would have motivated to lower the LDL concentration to below 55 mg/dl because LDL cholesterol concentration is inversely proportional to the regression of coronary atherosclerosis (coronary artery narrowing) i.e., the lower the LDL concentration, the greater the regression of coronary atherosclerosis. Therefore, lowering the LDL concentration would have been

reasonably to be useful in the method of reducing coronary artery stenosis, absent evidence to the contrary.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the instant specification, pages 10-29 have been considered, but are not found persuasive. No data in regard to the restenosis reduction is available for the evaluation of unexpected results. Among the 11 cases, only the lipid profile and the medications taken are revealed. The reduction of cholesterol in patients taking fish oil is an expected result based on the cited prior art. Therefore, no clear and convincing unexpected results are seen to be present herein.

Response to Arguments

Applicant's arguments filed July 30, 2002 averring the cited prior art's failure to teach all the limitations have been fully considered but they are not persuasive. When consider the cited prior art, as a whole, the cited prior art teaches all of the limitations herein. The cited prior art teaches all of the herein claimed ingredients are known to be useful as treating or preventing restenosis individually: fish oil, buspirone,

cholestyramine, niacin, and Aspirin are known to prevent or treat restenosis. Therefore, it flows logically to combine or incorporate agents, which are known to be useful individually for treating or preventing restenosis, into a single combination or method useful for the very same purpose. See *In re Kerkhoven* 205 USPQ 1069. Furthermore, the percentage of reduction of restenosis is exceeding 20% when treating with fish oil alone (See Sassen et al.).

Applicant's arguments filed July 30, 2002 averring Sassen et al.'s teaching of fish oil not showing any effects on restenosis have been considered but are not found persuasive. Applicants rely on the disclosure of Fincham et al. in page 187 of Sassen et al. However, this is only one study that is not shown fish oil as effective in regression of atherosclerosis. In page 186, col. 2, the Section of "Fish Oil and the Regression of Atherosclerosis" clearly states that pure regresision of experimental atherosclerosis lesions has been shown in ... leaving no doubt that relatively advanced lesions can reduce in size over time (Page 186, col. 2, second paragraph). Furthermore, several studies have shown that fish oil is effective in regression of human lesions (See page 186, col. 2, second paragraph). Moreover, in the conclusion Section in page 187, col. 2, Sassen et al. also disclosed that athersclerosis is a multi-factorial disease and it is apparent that in model where platelet aggregation is the dominant cause, fish oil is effective. When the immunological component of the atherogenesis dominates, fish oil is not. Therefore, such teachings are still meet the limitations of the instant claims.

Applicant's arguments filed July 30, 2002 averring Vane not providing motivation to combine aspirin and fish oil together have been considered, but are not found

persuasive. As discussed above, Vane et al. teaches that 50 – 1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet inhibition (See page 2588, col. 1, last, paragraph and page 2589, col. 1, last paragraph). Agents causing vasodilatation and platelet aggregation would have been reasonably expected to be useful in regression of atherosclerosis due to the role of platelet aggregation in atherogenesis. Moreover, aspirin would dilate the blood vessels, which is considered a direct counter effect of restenosis (narrowing). Combining two agents, which are known to be useful to treat restenosis individually, into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Applicant's arguments filed July 30, 2002 that even though two different agents can singly be used to treat the same condition, it does not necessarily mean that the combination of those agents would be further efficacious. These arguments have been considered but are not found persuasive. If different agents are known to treat the same condition individually, absent any evidence to the contrary, combining them into a single method of treating the very same conditions would be reasonably expected to be useful, at least an additive effect should be seen. For example, in Watts, treatment of diet plus a cholesterol-lowering agent is more effective in lowering MAWS than that of diet alone.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
October 24, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER

11/3/02